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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/819,266	03/28/2001	Agamemnon Antoniou Epenetos	JG-EPC-4955P/500563.20004	4300

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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	14

DATE MAILED: 12/31/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/819,266	EPENETOS, AGAMEMNON ANTONIOU	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *2,4-9,17-20 and 23-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,10-16,21 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's election without traverse of group I, claims 1, 3, 10-16, 21-22 in Paper No. 13 is acknowledged.

It is noted that although Applicant does not recite caspase-3, it is clear that group I encompasses caspase-3 and not caspase-6 or caspase-7.

Accordingly, claims 1, 3, 10-16, 21-22, caspase-3 is examined in the instant application.

OBJECTION

The specification is objected to because the arrangement of the specification is not according to 37 CFR 1.77(b), e.g. there is no proper order and heading for brief description of the drawings, and detailed description of the invention.

The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.

(b) CROSS-REFERENCE TO RELATED APPLICATIONS.

(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.

(d) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC (See 37 CFR 1.52(e)(5) and MPEP 608.05. Computer program listings (37 CFR 1.96(c)), "Sequence Listings" (37 CFR 1.821(c)), and tables having more than 50 pages of text are permitted to be submitted on compact discs.) or

REFERENCE TO A "MICROFICHE APPENDIX" (See MPEP § 608.05(a). "Microfiche Appendices" were accepted by the Office until March 1, 2001.)

(e) BACKGROUND OF THE INVENTION.

(1) Field of the Invention.

(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.

(f) BRIEF SUMMARY OF THE INVENTION.

(g) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).

(h) DETAILED DESCRIPTION OF THE INVENTION.

(i) CLAIM OR CLAIMS (commencing on a separate sheet).

(j) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).

(k) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if

the required "Sequence Listing" is not submitted as an electronic document on compact disc).

Claim Rejections - 35 USC § 112, SECOND PARAGRAPH

Claims 1, 3, 10-16, 21-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Claims 1, 3, 10-16, 21-22 are indefinite for the use of the language "substantially" in claim 1. The term "substantially" in claim 1 is a relative term which renders the claim indefinite. The term "substantially" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

2. Claims 1, 3, 10-16, 21-22 are indefinite, because it is not clear whether "a target-cell specific portion" refers to a portion that is specific for the target cell, such as a tumor specific antigen, or a ligand that selectively binds to the target cell.

3. Claim 14 is indefinite in the use of the language "variant", in that there is no discrete art recognizing the definition for this term.

Claim Rejections - 35 USC § 112, FIRST PARAGRAPH, WRITTEN DESCRIPTION

The following is a quotation of the first paragraph of 35 USC 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 14 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

Claim 14 is drawn to a compound comprising a target cell-specific portion and a cytotoxic portion, wherein the cytotoxic portion is a constitutively active variant of a naturally occurring caspase.

The specification discloses that "variant" "includes" cytotoxic portions comprising a naturally occurring caspase wherein there have been amino acid insertions, deletion

or substitutions, either conservative or non-conservative, such that the changes do not "substantially" reduce the apoptosis-inducing activity of the variant as compared to the naturally occurring caspase (p.11, first paragraph). Thus "variant" encompasses any compound resulted from insertions, deletion or substitutions, either conservative or non-conservative, of the naturally occurring caspase, wherein said variant does not necessarily have the apoptosis-inducing activity.

The specification discloses an example of caspase-3 and –6 variants taught by Srivivasula et al, 1998, wherein the subunits positions are reversed and rearranged, and wherein, different from the wild types, said variants are capable of autocatalytic processing (p.11, paragraph before last). The specification however further discloses that "constitutively active caspase" "includes" a protein or peptide which exhibits cyteine-bearing aspartate protease activity sufficient to induces apoptosis (p.10, second paragraph). Thus "constitutively active" variant does not necessarily retain the cyteine-bearing aspartate protease activity sufficient to induces apoptosis.

Although drawn specifically to the DNA art, the findings of *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412) are clearly relevant to the instant rejection. The court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the

court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

The claims 14 reads on variants of a caspase, wherein said variants have any type of substitution besides conservative substitution, at any amino acid, throughout the length of the peptide, as well as insertions and deletions. The specification and the claims do not place any limit on which amino acid to be subjected to conservative or non-conservative substitution, the type of substitution besides conservative substitution, nor the type of amino acids replacing the original amino acids. In addition, the specification and all other pending claims do not place any limit on the number of amino acids that could be substituted. Thus the scope of the claims includes numerous structural variants. Although the specification discloses that the types of changes are routinely done in the art, the specification and the claims do not provide any guidance as to which, or how many original amino acid(s) to be substituted, or to which type of substitution besides conservative substitution, or which amino acids could be deleted or inserted so that the claimed polypeptide could function as contemplated.. Structural features, that could distinguish the claimed variants from the polypeptide sequences known in the art, are missing from the disclosure. No common structural attributes that identify the claimed variants are disclosed. In addition, no common functional attributes that identify the claimed are disclosed, because the function of a polypeptidesequence could be abolished, even with substitution of only one amino acid of the polypeptide (Burgess et al. Journal of Cell Biology, 1990, 11: 2129-2138). In addition, although

conservative subsititution would not destroy the biological function of a protein, the specification fails to disclose which amino acid(s) would be subjected to conservative substitution. The general knowledge and level of skill in the art do not supplement the omitted description, because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the claimed variants, the structure of caspase-3 alone, and an example of caspase-3 and -6 variants, wherein the subunit positions are reversed and rearranged, are insufficient to describe said variants. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of variants. Thus, applicant was not in possession of the claimed variants.

Thus, there is insufficient support of claim 14 as provided by the Interim Written Description Guidelines published in the June 5, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645. Therefore, only a compound comprising a target cell-specific antibody and a cytotoxic portion, wherein the cytotoxic portion is a rearranged caspase-3, but not the full breadth of the claims meets the written description provision of 35 USC 112, first paragraph.

Claim Rejections - 35 USC § 112, FIRST PARAGRAPH, SCOPE

1. Claims 1, 3, 10-16, 21-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a compound comprising a target cell-specific antibody and a cytotoxic portion, wherein the cytotoxic portion is a rearranged caspase-3 that is capable of autocatalytic processing, does not reasonably provide

include claims 2, 3, 4, 15 - not required.

enablement for a compound comprising a "target cell-specific portion" and a cytotoxic portion, wherein the cytotoxic portion is a constitutively active caspase or a constitutively active variant of a naturally occurring caspase, or has substantially the same apoptosis-inducing activity as the caspase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1, 3, 10-16, 21-22 are drawn to for a compound comprising a "target cell-specific portion" and a cytotoxic portion, wherein the cytotoxic portion is a constitutively active caspase or a constitutively active variant of a naturally occurring caspase, or has substantially the same apoptosis-inducing activity as the caspase.

One cannot extrapolate the teaching of the specification to the scope of the claims because of the following reasons:

It is noted that a "target cell-specific portion" of claims 1, 10-16, 21-22 encompasses any protein that are specific for target cells, such as a tumor specific antigen, or a fragment of an antibody that is specific for the target cell, wherein said fragment does not necessarily bind to the antigen. Thus, one would not have expected that composition comprising any "target cell-specific portion" and a constitutively active caspase would be delivered to the target cells.

Further, the claims 1, 3, 10-15, 21-22, as written, encompass a compound comprising a "target cell-specific portion" and a cytotoxic portion, wherein the target cell-specific portion is mixed with the cytotoxic portion, and is not necessarily covalently conjugated to the cytotoxic portion. It would have been undue experimentation to use

the claimed compound because it is not clear how the constitutively active caspase could enter the cells without the ligand that binds to the target cells.

In view of the above, it would have been undue experimentation for one of skill in the art to practice the claimed invention.

2. Claims 1, 3, 10-16, 21-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a compound comprising a target cell-specific antibody and a cytotoxic portion, wherein the cytotoxic portion is a rearranged caspase-3 that is capable of autocatalytic processing, does not reasonably provide enablement for a compound comprising a target cell-specific portion and a cytotoxic portion, wherein the cytotoxic portion is "any constitutively active caspase" . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1, 3, 10-16, 21-22 are drawn to a compound comprising a target cell-specific portion and a cytotoxic portion, wherein the cytotoxic portion is a constitutively active caspase or a constitutively active variant of a naturally occurring caspase, or has substantially the same apoptosis-inducing activity as the caspase.

The specification discloses that a "constitutively active caspase" includes a protein or peptide which exhibits cyteine-bearing aspartate protease activity, p.10, second paragraph). The specification further discloses an example of "constitutively active caspases", i.e. caspase-3 and –6 variants taught by Srinivasula et al, 1998, JBC, 273 (17): 10107-11, wherein the subunits positions are reversed and rearranged, and

wherein, different from the wild types, said variants are capable of autocatalytic processing (p.11, paragraph before last). The specification also discloses that a fusion protein comprising scFv and a rearranged caspase could kill target cells *in vitro* (page 37-38 and figure 9).

Claims 1, 3, 10-16, 21-22 encompass a compound comprising a target cell-specific portion and a cytotoxic portion, wherein the cytotoxic portion is any constitutively active caspase, i.e. any protein or peptide which has any structure, provided it exhibits cyteine-bearing aspartate protease activity ,or any wild-type naturally occurring caspase, such as wild type effector caspase-3 or wild type initiator caspase-9, since it is well known in the art that effector and initiator caspases have cyteine-bearing aspartate protease activity.

One cannot extrapolate the teaching of the specification to the scope of the claims because it is unpredictable that a composition comprising a fusion of a target cell-specific portion and any "constitutively active caspase", i.e. any protein or peptide which has any structure, provided it exhibits cyteine-bearing aspartate protease activity, has the proper structure of the two subunits of caspase-3 to interdigitate and fold properly into the final active conformation, which is necessary for conferring the apoptosis inducing activity. Srinivasula et al, 1998, *supra*, teach that after cleavage at the conserved aspartate processing sites, the two subunits of caspase-3 interdigitate and fold properly into the final active conformation (p.10108, second column, first paragraph). Srinivasula et al, 1998, further teach that the caspase-3 and –6 variants have the C terminus of the LS region and the N terminus of the SS region free, and the

N terminus of the LS region and the C terminus of the SS region physically linked, thus enabling spontaneous folding into a fully active conformation that simulates the three-dimensional structure of the processed wild type molecule (p.10108, second column, first paragraph). In other words, proper conformation of the actived caspase-3 is required for caspase-3 to initiate apoptosis. Thus, one would not have expected that composition comprising a target cell-specific portion fused with any "constitutively active caspase" having any structure would be able fold into an active conformation necessary to induce apoptosis of target cells.

Moreover, MPEP 2164.08(a) teaches that a single means claim which covered every conceivable means for achieving the stated purpose was held nonenabling for the scope of the claims because the specification disclosed at most only those means known to the inventor. *In re Hyatt*, 708 F.2d 712, 714-715, 218 USPQ 195, 197 (Fed. Cir. 1983). In the instant application, the specification only discloses a single example of a "constitutively active caspase", i.e. caspase-3 and –6 variants taught by Srinivasula et al, 1998, *supra*, wherein the subunits positions are reversed and rearranged, and wherein, different from the wild types, said variants are capable of autocatalytic processing. However, the scope of the claim encompasses a compound comprising a target cell-specific portion and a cytotoxic portion, wherein the cytotoxic portion is any constitutively active caspase or any constitutively active variant of a naturally occurring caspase, and wherein said "constitutively active caspase" has any structure, provided it exhibits cyteine-bearing aspartate protease activity. Thus the claims would be non-enabled according to MPEP 2164.08(a).

Moreover, it is unpredictable that a fusion protein comprising a wild type effector caspase, such as caspase-3 would be effective in inducing apoptosis. Colussi PA et al, 1998, JBC, 273(41) : 26566-26570, teach that unlike an initiator caspase such as procaspase-2, an effector caspase such as procase-3 is a poor inducer of cell death, when transfected into mammalian cells, presumably because of its inability to autoactivate (p.26566, second column, second paragraph), and that artificially induced procaspase-3 oligomerization was necessary for its activation (p.26570, first column). Colussi et al further teach that fusion of procaspase-3 to the caspase-2 domain, which confers dimerization of procaspase molecules, converses procaspase-3 to an autoactivating caspase (abstract), i.e. a molecule effective in inducing apoptosis. Thus, one would not have expected that composition comprising a target cell-specific portion fused with a wild type effector caspase would be able to induce apoptosis of target cells, because of its inability to autoactivate.

Moreover, it is unpredictable that a fusion protein comprising any wild type initiator caspase, which has the oligomerizing abilty, could be effective in inducing apoptosis, because it is well known in the art that there exists several apoptosis agonists, such as members of the Bcl-2 family and CrmA that act upstream of the effector caspase-3 and-6, e.g. inhibition of the activation of the initiator caspase-9 (Colussi, PA et al, supra, p.26569, first column). Further, Gottschalk, AR et al, 1996, Cell Death and Differentiation, 3(1): 113-118, teach that overexpression of BAR, a well known apoptosis promoter, although can inhibit Bcl-2 from prolonging cell survival upon growth factor withdrawl, does not inhibit Bcl-XL from preventing apoptosis in a cell line

WEHI-231. Gottschalk, AR et al further teach that regulation of a cell's apoptotic threshold is likely to result from a complex set of interactions among Bcl-2 family members and other, as yet uncharacterized, regulators of apoptosis. Thus it is unpredictable that the activity of a fusion protein comprising any wild type initiator caspase would not be counteracted by the inhibitors of cell death, due to homeostasis mechanism in the target cells.

In view of the above, it would have been undue experimentation for one of skill in the art to practice the claimed invention.

3. Claims 1, 3, 10-16, 21-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a compound comprising a target cell-specific antibody and a cytotoxic portion, wherein the cytotoxic portion is a caspase-3 that is capable of autocatalytic processing, does not reasonably provide enablement for a compound comprising a target cell-specific portion and a cytotoxic portion, wherein the cytotoxic portion "has substantially the same apoptosis-inducing activity as the caspase". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 1, 3, 10-16, 21-22 are drawn to for a compound comprising a target cell-specific portion and a cytotoxic portion, wherein the cytotoxic portion "has substantially the same apoptosis-inducing activity as the caspase".

Claims 1, 3, 10-16, 21-22 encompass a compound comprising a target cell-specific portion and a cytotoxic portion, wherein the cytotoxic portion is any cell death agonist, such as BAR, BAD and BAX, which are notoriously well known in the art.

One cannot extrapolate the teaching of the specification to the scope of the claims because it is unpredictable that a compound comprising a target cell-specific portion and a cytotoxic portion, wherein the cytotoxic portion is any apoptosis agonists, such as BAR, BAD and BAX, would be able to induce apoptosis. It is notoriously well known in the art that several cell death antagonists such as Bcl-2, Bcl-XL and CrmA etc.. coexist with and could counteract cell death agonists. Gottschalk, AR et al, 1996, Cell Death and Differentiation, 3(1): 113-118, teach that overexpression of BAR, a well known apoptosis promoter, although can inhibit Bcl-2 from prolonging cell survival upon growth factor withdrawl, does not inhibit Bcl-XL from preventing apoptosis in a cell line WEHI-231. Gottschalk, AR et al further teach that regulation of a cell's apoptotic threshold is likely to result from a complex set of interactions among Bcl-2 family members and other, as yet uncharacterized, regulators of apoptosis. Thus it is unpredictable that the activity of a fusion protein comprising any apoptosis inducers would not be counteracted by the inhibitors of cell death, due to homeostasis mechanism in cells.

In view of the above, it would have been undue experimentation for one of skill in the art to practice the claimed invention.

4. Claims 21-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a compound comprising a target cell-specific

antibody and a cytotoxic portion, wherein the cytotoxic portion is a rearranged caspase-3 that is capable of autocatalytic processing, does not reasonably provide enablement for a "pharmaceutical composition" or a "compound for use in medicine", comprising a fusion of a target cell-specific portion and a cytotoxic portion, wherein the cytotoxic portion is a constitutively active caspase, or has substantially the same apoptosis-inducing activity as the caspase. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 21-22 are drawn to a pharmaceutical composition or a compound for use in medicine, comprising a fusion of a target cell-specific portion and a cytotoxic portion, wherein the cytotoxic portion is a constitutively active caspase, or has substantially the same apoptosis-inducing activity as the caspase.

Inherent in a pharmaceutical composition or a compound for use in medicine is *in vivo* use thereof.

The specification discloses *in vitro* killing of cells expressing CEA by a fusion protein comprising scFv and rearranged caspase-3 (pages 57-58 and figure 9). The specification further contemplates the use of the claimed fusion protein *in vivo* for treating cancer (p.51).

One cannot extrapolate the teaching of the specification to the claimed invention because there is no guidance on or exemplification of any correlation between killing of tumor cells *in vitro* and treating cancers *in vivo*. The *in vitro* experimental data presented, wherein the cells are constantly exposed to the claimed fusion protein, are

clearly not drawn to subjects with tumor cells and are not representative of in vivo conditions. It is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interations. Drexler et al (Leukemia and Lymphoma, 1993, 9:1-25) specifically teach, in the study of Hodgkin and Reed-Sternberg cancer cells in culture, that the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded and that only a few cell lines containing cells that resemble the *in-vivo* cancer cells have been established and even for the *bona fide* cancer cell lines it is difficult to prove that the immortalized cells originated from a specific cancer cell (see attached abstract). Further, Embleton et al (Immunol Ser, 1984, 23:181-207) specifically teaches that in procedures for the diagnosis of osteogenic sarcoma, caution must be used when interpreting results obtained with monoclonal antibodies that had been raised to cultured cell lines and specifically teach that cultured tumor cells may not be antigenically typical of the tumor cell population from which they were derived and it is well established that new artifactural antigens can occur as a result of culture (see attached abstract). Hsu (in Tissue Culture Methods and Applications, Kruse and Patterson, Eds, 1973, Academic Press, NY, see abstract, p.764) specifically teaches that it is well known that cell cultures *in vitro* frequently change their chromosomal constitutions (see abstract). The evidence presented clearly demonstrates that in cell culture systems, in general, and in cancer derived cell lines in particular, that artifactural chromosome constitutions and antigen expression are expected and must be taken into account when interpreting data

received from cell line assays. Further, Freshney (Culture of Animal Cells, A Manual of Basic Technique, Alan R. Liss, Inc., 1983, New York, p4) teach that it is recognized in the art that there are many differences between cultured cells and their counterparts *in vivo*. These differences stem from the dissociation of cells from a three-dimensional geometry and their propagation on a two-dimensional substrate. Specific cell interactions characteristic of histology of the tissue are lost. The culture environment lacks the input of the nervous and endocrine systems involved in homeostatic regulation *in vivo*. Without this control, cellular metabolism may be more constant *in vitro* but may not be truly representative of the tissue from which the cells were derived. This has often led to tissue culture being regarded in a rather skeptical light (p. 4, see Major Differences *In Vitro*). Further, Dermer (Bio/Technology, 1994, 12:320) teaches that,

petri dish cancer is a poor representation of malignancy, with characteristics profoundly different from the human disease Further, Dermer teaches that when a normal or malignant body cell adapts to immortal life in culture, it takes an evolutionary - type step that enables the new line to thrive in its artificial environment. This step transforms a cell from one that is stable and differentiated to one that is not, yet normal or malignant cells *in vivo* are not like that. The reference states that evidence of the contradictions between life on the bottom of a lab dish and in the body has been in the scientific literature for more than 30 years. Clearly it is well known in the art that cells in culture exhibit characteristics different from those *in vivo* and cannot duplicate the complex conditions of the *in vivo* environment involved in host-tumor and cell-cell interations. Thus, based on the cell culture data presented in the specification, it could

not be predicted that, in the *in vivo* environment, the claimed fusion protein would be effective in killing tumor cells.

In addition, one cannot extrapolate the teaching of the specification to the claims because it is well known that the art of anticancer drug discovery for cancer therapy is highly unpredictable, for example, Gura (Science, 1997, 278:1041-1042) teaches that researchers face the problem of sifting through potential anticancer agents to find ones promising enough to make human clinical trials worthwhile and teach that since formal screening began in 1955, many thousands of drugs have shown activity in either cell or animal models but that only 39 have actually been shown to be useful for chemotherapy (p. 1041, see first and second para). Because of the known unpredictability of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the claimed fusion protein would be effective in treating cancers. Further, the refractory nature of cancer to drugs is well known in the art. Jain (Sci. Am., 1994, 271:58-65) teaches that tumors resist penetration by drugs (p.58, col 1) and that scientists need to put expanded effort into uncovering the reasons why therapeutic agents that show encouraging promise in the laboratory often turn out to be ineffective in the treatment of common solid tumors (p. 65, col 3). Curti (Crit. Rev. in Oncology/Hematology, 1993, 14:29-39) teaches that solid tumors resist destruction by chemotherapy agents and that although strategies to overcome defense mechanisms of neoplastic cells have been developed and tested in a number of patients, success has been limited and further teaches that it is certainly possible that cancer cells possess many as yet undefined additional molecular mechanisms to defeat chemotherapy

treatment strategies and if this is true, designing effective chemotherapeutic regimens for solid tumors may prove a daunting task (para bridging pages 29-30) and concludes that knowledge about the physical barriers to drug delivery in tumors is a work in progress (p. 36, col 2). It is clear that based on the state of the art, in the absence of experimental evidence, no one skilled in the art would accept the assertion that the claimed fusion protein would be effective in treating cancers. In addition, Hartwell et al (Science, 1997, 278:1064-1068) teach that an effective chemotherapeutic must selectively kill tumor cells, that most anticancer drugs have been discovered by serendipity and that the molecular alterations that provide selective tumor cell killing are unknown and that even understanding the detailed molecular mechanism by which a drug acts often provides little insight into why the treated tumor cell dies (para bridging pages 1064-1065) and Jain (cited supra) specifically teaches that systemic treatment typically consists of chemotherapeutic drugs that are toxic to dividing cells (p. 58, col 2, para 2).

In view of the above, it would have been undue experimentation for one of skill in the art to practice the claimed invention.

5. Claim 14 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a compound comprising a target cell-specific antibody and a cytotoxic portion, wherein the cytotoxic portion is a rearranged caspase-3 that is capable of autocatalytic processing, does not reasonably provide enablement for a compound comprising a target cell-specific antibody and a cytotoxic portion, wherein the cytotoxic portion is constitutively active "variant" of a naturally occurring

caspase . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 14 is drawn to a compound comprising a target cell-specific portion and a cytotoxic portion, wherein the cytotoxic portion is a constitutively active "variant" of a naturally occurring caspase.

The specification discloses that "variant" "includes" cytotoxic portions comprising a naturally occurring caspase wherein there have been amino acid insertions, deletion or substitutions, either conservative or non-conservative, such that the changes do not "substantially" reduce the apoptosis-inducing activity of the variant as compared to the naturally occurring caspase (p.11, first paragraph). Thus "variant" encompasses any compound resulted from insertions, deletion or substitutions, either conservative or non-conservative, of the naturally occurring caspase, wherein said variant does not necessarily have the apoptosis-inducing activity.

The specification discloses an example of caspase-3 and –6 variants taught by Srivivasula et al, 1998, wherein the subunits positions are reversed and rearranged, and wherein, different from the wild types, said variants are capable of autocatalytic processing (p.11, paragraph before last). The specification however further discloses that "constitutively active caspase" "includes" a protein or peptide which exhibits cyteine-bearing aspartate protease activity sufficient to induces apoptosis (p.10, second paragraph). Thus "constitutively active" variant does not necessarily retain the cyteine-bearing aspartate protease activity sufficient to induces apoptosis.

The scope of the claim includes numerous structural variants. Applicants have not shown how to make and use the claimed variants which are capable of functioning as that which is being disclosed.

Protein chemistry is probably one of the most unpredictable areas of biotechnology. Such unpredictability would equally apply to DNA sequences which encode proteins. For example, replacement of a single lysine residue at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein (Burgess et al. Journal of Cell Biology, 1990, 11: 2129-2138). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (Lazar et al. Molecular and Cell Biology, 1988, 8: 1247-1252). Similarly, it has been shown that aglycosylation of antibodies reduces the resistance of the antibodies to proteolytic degradation, while CH2 deletions increase the binding affinity of the antibodies (see Tao. et al. The Journal of Immunology, 1989, 143(8): 2595-2601, and Gillies et al. Human Antibodies and Hybridomas, 1990, 1(1): 47-54). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein.

In view of the above unpredictability, one of skill in the art would be forced into undue experimentation in order to perform the claimed invention as broadly as claimed.

In addition, although conservative subsititution would not destroy the biological function of a protein, the specification fails to disclose which amino acid(s) would be subjected to conservative substitution. In the absence of a source of method of making such variants, one of skill in the art would be forced into undue experimentation to practice the claimed invention as broadly as claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 22 are rejected under 35 U.S.C. 102(b) as being anticipated by US 5,994,313.

Claims 1, 22 are drawn to a compound or a compound for use in medicine, comprising a target cell-specific portion and a cytotoxic portion, wherein the cytotoxic portion has substantially the same apoptosis-inducing activity as the caspase.

Claim 22 recites the claimed fusion protein for use in medicine. However, this limitation is viewed as a recitation of intended use and therefore is not given patentable weight in comparing the claims with the prior art. Claim 22 reads on the ingredient *per*

se, which is a fusion protein comprising a target cell-specific portion and a cytotoxic portion, wherein the cytotoxic portion has substantially the same apoptosis-inducing activity as the caspase.

US 5,994,313 teaches a method for inducing apoptosis in a cell which expresses one DNA construct encoding a chimeric protein (claim 1), said protein comprises a ligand-binding domain, which comprises an antibody (claim 15), and an action domain, which comprises a cytoplasmic domain of a human Fas antigen sufficient to induce apoptosis in a cell following oligomerization of the chimeric protein.

Thus the fusion protein taught by US 5,994,313 seems to be the same as the claimed compound.

The reference does not specifically teach a compound comprising a target cell-specific portion and a cytotoxic portion, wherein the cytotoxic portion has substantially the same apoptosis-inducing activity as the caspase. However, the claimed compound appears to be the same as the prior art chimeric protein. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable diffrences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

1. Claim 21 is rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,994,313 in view of Johnstone and Thorpe (Immunochemistry in Practice, 2nd Ed., 1987, Blackwell Scientific Publications, Oxford, pages 49-50).

Claim 21 is drawn to a pharmaceutical compound, comprising a target cell-specific portion and a cytotoxic portion, wherein the cytotoxic portion has substantially the same apoptosis-inducing activity as the caspase and a pharmaceutically acceptable carrier.

Claim 21 recites the claimed compound formulated in a pharmaceutical composition. However, this limitation is viewed as a recitation of intended use and therefore is not given patentable weight in comparing the claims with the prior art. The claim reads on the ingredient *per se*, which is a fusion protein comprising a target cell-specific portion and a cytotoxic portion, wherein the cytotoxic portion has substantially the same apoptosis-inducing activity as the caspase.

The teaching of US 5,994,313 has been set forth above. US 5,994,313 however does not teach a pharmaceutically acceptable carrier.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to include a carrier in the composition because Johnstone and Thorpe teach that it was common practice in the art at the time of applicant's invention to formulate compositions of antibodies and PBS, which is considered to be an acceptable carrier for storage of antibodies, p. 49 and 50. One of ordinary skill would have been motivated to do so in order to develop compositions suitable for storage.

Finally, it has been held by the Court that a compound and a carrier are obvious, if it is obvious in the art to utilize a carrier with related compounds. See *In re Rosicky*, 125

2. Claims 1, 3, 10-16, 21-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Srinivasula et al, 1998, *supra*, in view of US 4,753,894 and Colussi, PA et al, 1998, *supra*.

Claims 1, 3, 10-16 are drawn to for a compound comprising a fusion protein of a target cell-specific portion and a cytotoxic portion, wherein the cytotoxic portion is a constitutively active caspase or a constitutively active variant of a naturally occurring caspase, or has substantially the same apoptosis-inducing activity as the caspase. The target cell-specific portion recognizes and selectively binds to a tumor cell antigen. The cytotoxic portion is a constitutively active effector caspase-3. The cytotoxic portion is of mammalian origin and is capable of oligomerization.

Claims 21 and 22 are drawn to a pharmaceutical composition or a compound for use in medicine, comprising a fusion of a target cell-specific portion and a cytotoxic portion, wherein the cytotoxic portion is a constitutively active caspase, or has substantially the same apoptosis-inducing activity as the caspase.

Claims 21-22 recite the claimed compound formulated in a pharmaceutical composition or a compound for use in medicine. However, this limitation is viewed as a recitation of intended use and therefore is not given patentable weight in comparing the claims with the prior art. The claims read on the ingredient *per se*, which is a fusion protein comprising a target cell-specific portion and a cytotoxic portion, wherein the

cytotoxic portion is a constitutively active caspase, or has substantially the same apoptosis-inducing activity as the caspase.

Srinivasula et al teach constitutively active variants of caspase-3 and –6, wherein the subunits positions of the caspase are reversed and rearranged, and wherein, different from the wild types, said variants are capable of autocatalytic processing. Srinivasula et al further teach that since caspase-3 and –6 are the most downstream executioners of apoptosis, the constitutively active variants of caspase-3 and 6 could be used at very low concentration to induce apoptosis in target tissues or tumors (abstract).

US 4,753,894 teach how to make an immunotoxin comprising an antibody specific for breast cancer and a cytotoxic portion comprising ricin A chain for targeting to breast cancer cells.

Colussi PA et al, 1998, JBC, 273(41) : 26566-26570, teach that unlike an initiator caspase such as procaspase-2, an effector caspase such as procase-3 is a poor inducer of cell death, when transfected into mammalian cells, presumably because of its inability to autoactivate (p.26566, second column, second paragraph), and that artificially induced procaspase-3 oligomerization was necessary for its activation (p.26570, first column). Colussi et al further teach that fusion of procaspase-3 to the caspase-2 domain, which confers dimerization of procaspase molecules, converses procaspase-3 to an autoactivating caspase (abstract), i.e. a molecule effective in inducing apoptosis. Colussi et al also teach that apoptosis inhibitors such as MIHA and P35 inhibit the induction of apoptosis by said fusion protein of procaspase-3 to an oligomerizing domain of caspase-2 by inhibiting procaspase processing, and that Bcl-2

does not inhibit the processing of said fusion protein, because Bcl-2 acts upstream of caspase-3 by inhibiting the activation of caspase-9 (p.26569, first column).

It would have been *prima facia* obvious to a person of ordinary skill in the art at the time the invention was made to make a fusion protein comprising the constitutively active variants of caspase-3 and –6 as taught by Srinivasula et al, and an antibody that specifically binds to a tumor cell, using the method taught by US 4,753,894, for targeting to tumor cells, because of the following reasons: 1) The constitutively active variants of caspase-3 and 6 could be used at very low concentration to induce apoptosis in target tissues or tumors, as taught by Srinivasula et al, 2) Since caspase-3 and –6 are the most downstream executioners of apoptosis, a fusion protein comprising caspase-3 would not be inhibited by an apoptosis inhibitor, such as Bcl-2, as taught by Colussi et al, and 3) The constitutively active variants of caspase-3 and 6, as taught by Srinivasula et al, are used and not the wild type caspase-3 or an initiator caspase such as caspase-9, because of the following reasons: An effector caspase such as wild type procase-3 is a poor inducer of cell death, when transfected into mammalian cells, presumably because of its inability to autoactivate, as taught by Colussi et al. Further, while caspase-3 *per se* is not the target of the apoptosis inhibitor Bcl-2, the initiator caspase, such as caspase-9 is the target of the apoptosis inhibitor Bcl-2, as taught by Colussi et al, which could counteract the action of the initiator caspase-9. In addition, the variant of capase-3 taught Srinivasula et al would be advantageous, because it is capable of autoactivation, i.e., already has the conformation necessary for its induction of apoptosis, and does not require further oligomerization, whereas wild type caspase-3

could be inhibited by apoptosis inhibitors such as MIHA and P35, which inhibit the induction of apoptosis by inhibiting procaspase processing, i.e. oligomerization of caspase-3, as taught by Colussi et al.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 703-305-2008. The examiner can normally be reached on 9:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, ANTHONY CAPUTA can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0916.

SUSAN UNGAR, PH.D
PRIMARY EXAMINER

MINH TAM DAVIS

December 8, 2002